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<p>(54) Title: TREATMENT OF EOSINOPHIL-ASSOCIATED PATHOLOGIES, SUCH AS BRONCHIAL ASTHMA, WITH SYNERGISTIC COMBINATIONS OF GLUCOCORTICOIDS AND A LOCAL ANESTHETICS</p> <p>(57) Abstract</p> <p>A therapeutic method is provided to treat an eosinophil-associated pathology, such as bronchial asthma, by administering to a mammal in need of such treatment, an effective amount of at least one topical anesthetic, such as lidocaine, with an effective amount of one or more glucocorticoids, or the pharmaceutically acceptable salts thereof.</p>															
<p>The graph plots Viability (%) on the y-axis (0 to 100) against DAY on the x-axis (0, 2, 4). Two data series are shown: MEDIUM (dashed line with open circles) and LIDOCaine-0.25mg/mL (solid line with solid circles). The MEDIUM curve remains at 100% viability. The LIDOCaine curve starts at 100% at day 0 and decreases to approximately 30% at day 4.</p> <table border="1"> <thead> <tr> <th>DAY</th> <th>MEDIUM (%)</th> <th>LIDOCaine (%)</th> </tr> </thead> <tbody> <tr> <td>0</td> <td>100</td> <td>100</td> </tr> <tr> <td>2</td> <td>100</td> <td>82</td> </tr> <tr> <td>4</td> <td>100</td> <td>30</td> </tr> </tbody> </table>				DAY	MEDIUM (%)	LIDOCaine (%)	0	100	100	2	100	82	4	100	30
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TREATMENT OF EOSINOPHIL-ASSOCIATED PATHOLOGIES, SUCH AS BRONCHIAL ASTHMA, WITH SYNERGISTIC COMBINATIONS OF GLUCOCORTICOIDS AND A LOCAL ANESTHETICS

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Background of the Invention

For many years, bronchial asthma was regarded as an abnormality of respiratory smooth muscle in which afflicted individuals experience the onset of bronchospasm as a consequence of overactivity of the bronchial smooth muscle. Later, the bronchial mast cell was thought to play a critical role in the stimulation of bronchial smooth muscle by producing leukotriene C4 (the slow-reacting substance of anaphylaxis) and histamine, which cause contraction. However, over the past few years, a dramatic change in thinking regarding the pathophysiology of bronchial asthma has occurred and the involvement of eosinophilic leukocytes, or "eosinophils", in the inflammation of the airway has been suspected.

Eosinophils are a type of leukocyte containing cytoplasmic granules that stain strongly with acidic dyes. Eosinophils have been associated with bronchial asthma since the early part of this century and they are characteristically found in large numbers in the lung tissue of patients dying of asthma (Ellis et al., J. Med. Sci., 136, 407 (1908)). In the mid 1970's, it was demonstrated that the severity of bronchial asthma can be related to the number of eosinophils in the peripheral blood of the patients (Horn et al., N. Engl. J. Med., 292 1152 (1975)).

Also around this time, studies of eosinophils had shown the presence of basic (cationic) granule proteins. One of the principal proteins associated with eosinophil granules, the major basic protein (MBP), was so-named because, in the guinea pig it comprises more than 50% the granule protein, is strongly basic (arginine-rich), and is proteinaceous (Gleich, J. Exp. Med., 137, 1459 (1973); Wasmoen et al., J. Biol. Chem., 263, 12559 (1988)). MBP is toxic to worms (helminths) and mammalian cells, and causes damage to bronchial respiratory epithelium (Gleich et al., Adv. Immunol., 39, 177 (1986)).

For example, direct application of MBP to respiratory epithelium in concentrations as low as 10 μ g/ml (7.1×10^{-7} M) causes ciliostasis and epithelial damage. This damage consists of desquamation of epithelial cells into the lumen of the respiratory tract, as well as frank disruption of epithelial cells. The effects

of MBP are dose-related and higher doses cause damage more quickly and to a greater extent than lower doses (Frigas et al., Lab. Invest., 42, 35 (1980)). These effects are caused both by MBP from guinea pig eosinophils and from human eosinophils, and impact both guinea pig and human respiratory tissues (Gleich et al., J. Immunol., 123, 2925 (1979); Frigas et al., Mayo Clin. Proc., 56, 345 (1981)).

The ciliostasis, desquamation of respiratory epithelial cells, and damage to the respiratory epithelial cells caused by MBP are suggestive of the pathologic changes observed in bronchial asthma. In bronchial asthma an exudate of 10 eosinophils, normal and degenerating bronchial epithelial cells, and clumps of epithelial cells, referred to as Creola bodies, are present in the bronchial lumen. In the bronchial mucosa and submucosa, edema, separation and shedding of ciliated cells, and eosinophil infiltration are seen. Thus, the effects of the 15 eosinophil granule MBP *in vitro* are similar to the pathology characteristic of bronchial asthma (Dunnill, J. Clin. Path., 13, 27 (1960)).

Because of this discovery, the levels of MBP in sputum of patients with bronchial asthma were measured to determine whether they were elevated and to what degree. Levels of MBP in sputum samples from 206 patients with various respiratory diseases were measured by radioimmunoassay. In 165 of these 20 patients, MBP was not measurable or the concentrations of MBP were less than 0.1 $\mu\text{g}/\text{ml}$. In these 165 patients, only one patient carried the diagnosis of asthma. Among 41 patients with sputum concentrations of MBP greater than 0.1 $\mu\text{g}/\text{ml}$, 28 were diagnosed as having asthma and in the remaining 13 patients, six had obstructive lung disease which is often confused with asthma. In 15 patients 25 hospitalized for treatment of asthma, sputum MBP levels ranged from 0.5 (0.04 $\times 10^{-6}$ M) to 93 $\mu\text{g}/\text{ml}$ (6.6×10^{-6} M) (geometric mean 7.1 $\mu\text{g}/\text{ml}$, 0.51×10^{-6} M). Further, the levels of sputum MBP in these 15 patients declined during therapy 30 with glucocorticoids (Frigas et al., Mayo Clinic. Proc., 56, 345 (1981)). These results indicated that MBP levels in the toxic range were present in the sputum of patients with asthma, that levels of sputum MBP were highest in acutely ill patients, and that sputum MBP levels decline after steroid therapy.

The possibility that MBP directly causes damage to bronchial epithelium was tested utilizing immunofluorescence localization of MBP in lung tissues of patients dying of asthma (Filley et al., Lancet, 2, 11 (1982)). Patients dying of asthma had the classical pathologic features of bronchial asthma, including a 5 thickened basement membrane zone, goblet cell hyperplasia, and peribronchial inflammatory infiltrates with eosinophils in the lamina propria. Examination of these same sections by immunofluorescence to localize MBP, revealed MBP deposition onto damaged bronchial epithelium. These results demonstrate that MBP was released from the eosinophil and was present in tissues at the site of 10 damage.

Subsequent studies extended these observations showing that not only MBP, but two of the other cationic eosinophil granule proteins, namely eosinophil peroxidase (EPO) and eosinophil cationic protein (ECP), have the capacity to damage bronchial epithelium (Motojima et al., Am. Rev. Respir. Dis., 139, 801 (1989)). Analyses of the effect of MBP on respiratory epithelium showed that although MBP reduced the frequency of ciliary beating, its predominant effect was to reduce the number of beating ciliated cells. The effect of MBP in causing cessation of ciliary beating was seen in respiratory epithelial cells in the epithelium itself as well as in axonemes (the contractile elements of 15 the cilia)(Hastle et al., Am. Rev. Resp. Dis., 135, 845 (1987)).

One of the signal abnormalities in bronchial asthma is bronchial hyperactivity. Bronchial hyperactivity is manifested in patients as a marked irritability of the respiratory tract to nonspecific stimuli including cold air, dust, and, in the laboratory, to inhaled methacholine. Indeed, this hyperactivity is a 25 diagnostic criterion for asthma (N.J. Gross et al., in Allergy, Principles and Practice, Vol. I., E4 Middleton, Jr. et al., eds. (1988) at page 790). Analyses of MBP in the lung secretions of patients with asthma (obtained by lavage of the bronchi and alveoli) showed that MBP levels in lung fluids are correlated with bronchial hyperactivity (Wardlaw et al., Am. Rev. Resp. Dis., 137, 62 (1988)). 30 In cynomolgus monkeys, provocation of inflammation rich in eosinophils was associated with an increase in bronchial hyperactivity and with the presence of MBP in lung secretion; both the numbers of eosinophils and the MBP

concentration were significantly correlated with bronchial hyperactivity to methacholine (Gundel et al., J. Appl. Physiol., 68, 779 (1990)).

At the molecular level, eosinophil proliferation and differentiation are regulated by various cytokines, such as IL-3, IL-5 and GM-CSF. See Silberstein et al., Hematol. Oncol. Clin. North Am., 3, 511 (1989). These cytokines, as well as IFN- γ , have been shown to prolong survival of eosinophils *in vitro* by Valerius et al., J. Immunol., 145, 2950 (1990), and to augment eosinophil function (Rothenberg et al., J. Clin. Invest., 81 1986 (1988); Fujisawa et al., J. Immunol., 144, 642 (1990); Silberstein et al., J. Immunol., 137, 3290 (1986)).

10 Furthermore, IL-5 primes eosinophils for enhanced locomotor responses to chemotactic agents, such as platelet-activating factor, leukotriene B4, and IL-8 (Sehmi et al., Blood, 79, 2952 (1992)). Also, recent information indicates that IL-5 is present in the lung following allergen-induced pulmonary late allergic reactions (Sedgwick et al., Am. Rev. Respir. Dis., 144, 1274 (1991)) and mRNA for IL-5 is expressed in the bronchial epithelium of patients with asthma (Hamid et al., J. Clin. Invest., 87, 1541 (1991)). These observations suggest that the inflammation associated with asthma is critically dependent on the presence of cytokines, especially IL-5, and recent data showing that antibodies to IL-5 block both antigen-induced eosinophilia and antigen-induced bronchial hyperactivity

15 support that view (Mauser et al., Am. Rev. Respir. Dis., 145, A859 (1992)).

Glucocorticoids are the most useful class of drugs for treating many eosinophil-related disorders, including bronchial asthma (Schleimer et al., Am. Rev. Respir. Dis., 141, 559 (1990)). They produce eosinopenia in normal persons, decrease circulating eosinophils in patients with eosinophilia, and

20 reduce eosinophil influx at inflammatory sites (Butterfield et al., in Antiinflammatory Steroid Action: Basic and Clinical Aspects, Schleimer et al., eds. Academic Press, Inc. (1989) at p. 151. The mechanism of these effects is still uncertain. Lamas et al. in J. Immunol., 142, 3978 (1989) and J. Allergy Clin. Immunol., 85, 282 (1990) have reported that supernatants from human

25 vascular endothelial cells cultured with glucocorticoids had reduced eosinophil survival-enhancing activity *in vitro*.

Recently, Wallen et al., J. Immunol., 147, 3940 (1991) reported the dose-dependent inhibition of IL-5-mediated eosinophil survival by dexamethasone, methylprednisolone and hydrocortisone, and the inhibition of IL-3-, GM-CSF-, and IFN- γ -mediated eosinophil survival by dexamethasone. Dexamethasone

5 produced a dose-dependent increase in the EC₅₀ for IL-5-mediated viability enhancement. The relative eosinophil viability inhibitory potencies of the glucocorticoids tested correlated with previously described antiinflammatory potencies and with the affinities for the glucocorticoid receptor: dexamethasone > methylprednisolone > hydrocortisone.

10 For many patients with asthma, glucocorticoids are the principal therapy and these patients may require glucocorticoid therapy for long periods of time, e.g., months to years. In fact, the disease can be characterized as one of chronic glucocorticoid toxicity, in that the toxicity of these steroids can cause severe morbidity and even mortality in the patients. Furthermore, cessation of

15 glucocorticoid therapy leads to withdrawal symptoms, such as malaise and muscle pain. However, presently glucocorticoids are the only effective therapy for severe asthma, and are prescribed long-term despite their toxicity.

The information discussed above pertains to bronchial asthma and the role of toxic eosinophil granule proteins exemplified by MBP in the

20 pathophysiology of bronchial asthma. Evidence exists that these toxic proteins also contribute to the pathogenesis of diseases associated with eosinophil infiltration in the upper respiratory tract. For example, Ayars et al. in Am. Rev. Resp. Dis., 140, 125 (1989), have reported that MBP is toxic to respiratory epithelium from the nose, and Bascom et al., in J. Allergy Clin. Immunol., 84,

25 338 (1989) found that elevated MBP concentrations are present in nasal fluids following experimental hay fever. As reported by Harlin et al., J. Allergy Clin. Immunol., 81, 867 (1988), MBP is deposited on respiratory epithelium of the upper airway in association with damage to the epithelium. Therefore, toxic eosinophil granule proteins may cause disease of the upper airway in the same

30 manner as they likely do in the lower airway in the case of bronchial asthma..

Finally, Udell et al., in Am. J. Ophthalmol. 92, 824 (1981) reported that MBP is elevated in tears of patients with vernal conjunctivitis, a form of allergic

inflammation of the eye, and Trocme et al., in Am. J. Ophthalmol., **108**, 57 (1989) found that MBP is deposited into inflamed conjunctiva of such patients. Thus, evidence exists that MBP may act as a toxin to the conjunctiva.

Therefore, a need exists for improved therapeutic methods to treat 5 pathologies, such as bronchial asthma, which are caused by, or aggravated by, eosinophils or the toxic proteins released by eosinophils.

Summary of the Invention

The present invention provides a method for treating a pathology characterized by elevated levels of eosinophils (i.e., an eosinophil-associated 10 pathology) comprising co-administering to a mammal in need of such treatment an amount of a topical anesthetic and an amount of a glucocorticoid, wherein said amounts are effective to counteract at least one of the symptoms of said pathology. It is preferred that the mammal be a human, such as a patient afflicted with bronchial asthma.

15 As used herein, the terms "co-administer" or "co-administration" are defined to encompass administration simultaneously, as in admixture in a single composition, or sequentially, so that they are delivered to, and present at, the target site *in vivo*, together in therapeutically effective amounts.

Gleich et al. (US Patent No. 5,510,339) discloses the use of topical 20 anesthetics to reduce dependence of asthma patients on steroid therapy. In contrast, the present invention is based on Applicant's surprising discovery that lidocaine and dexamethasone act synergistically to inhibit human eosinophil survival *in vitro*. That is, the administration of a combination of a topical anesthetic and a glucocorticoid requires less of either agent for therapeutic 25 efficacy than would be expected to be required on the basis of an additive effect. Thus, the treatment of eosinophil-associated diseases with a combination of topical anesthetics and glucocorticoids is more effective than treatment with either agent alone.

A preferred embodiment of the present method is directed to a therapy for 30 bronchial asthma, eosinophil-associated intranasal inflammation, including nasal polyps, inflammation of the paranasal sinuses and allergic rhinitis, eosinophil-associated cutaneous inflammation, eosinophil-associated disorders of the

gastrointestinal tract, such as inflammatory bowel disease, and eosinophil-associated inflammation of the eye, such as vernal and allergic conjunctivitis. For example, the present invention provides a therapy for bronchial asthma and the other hypersensitivity diseases of the respiratory tract, by topical 5 administration, e.g., by inhalation or insufflation of a composition comprising a topical anesthetic, such as lidocaine, bupivacaine, etidocaine, tetracaine and the like, and a glucocorticoid. The topical anesthetic in turn is able to inhibit the activity of eosinophil-active cytokines, such as IL-5, and thus, to limit the negative effects of eosinophils on respiratory epithelium or other tissue. The 10 activity of the topical anesthetic is effectively enhanced by the co-administration of the glucocorticoid. Topical administration of the composition of the present invention, e.g., in nose drops or eye drops, can relieve the symptoms or conditions due to eosinophil-associated inflammation of the nasal passages or of the eye, such as allergic rhinitis or allergic conjunctivitis.

15 The present invention also provides the use of a combination of a topical anesthetic and a glucocorticoid to prepare a medicament for treating an eosinophil-associated pathology in a mammal.

The present invention further provides a pharmaceutical composition comprising a combination of a topical anesthetic and a glucocorticoid in an 20 amount effective to counteract at least one of the symptoms of an eosinophil-associated pathology.

As used herein, the term topical anesthetic or glucocorticoid encompasses the free compounds, as well as the pharmaceutically acceptable salts thereof.

Brief Description of Drawings

25 Figure 1 is a graphical depiction of the time course of eosinophil viability inhibition effect by lidocaine. Culture medium was supplemented with recombinant human interleukin 5 (rhIL-5), 10 pg/ml, and the effects on eosinophil viability of lidocaine (0.25 mg/ml)(•), or medium control (Hybri-Care ®) (American Type Culture Collection, Rockville, MD) containing 30 gentamicin, 50 µg/ml and 10% defined calf serum (Hyclone Laboratories, Logan, UT) were tested by comparing viabilities at two and four days.

Figure 2 is a graphical depiction of the inhibition of eosinophil survival mediated by cytokines with lidocaine. Purified eosinophils were tested in the eosinophil survival assay for four days and their viability determined by staining with propidium iodide and analysis by FACS.

5 Figure 3 is a graphical depiction of the drug regimen of Patient A with respect to inhaled triamcinolone (Panel A), inhaled lidocaine (Panel B) and oral prednisone (Panel C).

Figure 4 is a graphical depiction of the drug regimen of Patient B with respect to inhaled budesonide (Panel A), inhaled lidocaine (Panel B) and oral 10 prednisone (Panel C).

Figure 5 is a graphical depiction of the effect of lidocaine and dexamethasone on cytokine-mediated eosinophil survival. Isolated eosinophils were incubated in 96-well plates at 2.5×10^5 /mL with varying concentrations of IL-5 plus or minus drugs (LC = lidocaine, Dex = dexamethasone, nil = control) 15 in a total volume of 200 μ l Hybri-Care® medium. After four days of culture, percent eosinophil (EO) survival was determined.

Detailed Description of the Invention

Eosinophil-Associated Pathologies

In addition to the hypersensitivity diseases discussed above, such as 20 bronchial asthma, nasal inflammation and conjunctivitis, many other conditions associated with elevated levels of eosinophil activation and accumulation, some of which are presently treated with glucocorticoids, are amenable to treatment by the present combination therapy. These conditions include, but are not limited to, chronic eosinophilic pneumonia, allergic rhinitis, allergic sinusitis, allergic 25 gastroenteropathy, eosinophilic gastroenteritis, atopic dermatitis, bullous pemphigoid, episodic angiodema associated with eosinophilia, ulcerative colitis, inflammatory bowel disease, vernal conjunctivitis, giant papillary conjunctivitis, and allergic conjunctivitis.

Topical Anesthetics

30 Topical anesthetics, all of which are believed to be useful in the present invention, are an art-recognized class of drugs which temporarily interrupt mammalian nerve transmissions. They can generally be grouped into two

chemical classifications structurally; the N-arylamides or carboxamides, such as lidocaine; and the aminoalkylbenzoates, such as procaine, benoxinate and proparacaine. Preferred N-arylamides comprise the N-(C₇-C₂₂)arylamides of amino-substituted (C₁-C₅)carboxylic acids, e.g., N-[(mono or di-(C₁-C₄)alkyl)phenyl]amides of aliphatic (C₁-C₅)carboxylic acids, which acids are preferably substituted with the moiety (R)(R¹)N- wherein R is H or (C₁-C₅)alkyl and R¹ is (C₁-C₅)alkyl. For example, a preferred carboxylic acid can have the general formula (R)(R¹)N(X)CO₂H where R and R¹ are as defined above and X is a branched- or straight-chain (C₁-C₅)alkylene group such as 1,1-ethylene, 1,2-ethylene, methylene, 2,2-propylene, 1,3-propylene, and the like. Another preferred class of N-arylamides are the N-[(mono- or di- (C₁-C₄) alkyl) phenyl]amides of 5- or 6-membered-heterocycloaliphatic carboxylic acids, which acids comprise one or two [(C₁-C₄)alkyl- substituted]N atoms, i.e., N-butylpiperidine-2-carboxylic acid.

15 The aminoalkylbenzoates include esters between benzoic acids and alcohols of the general formula (R⁴)(R⁵)N(X)OH, wherein X is as defined above, R⁴ is H or (C₁-C₄)-alkyl, R⁵ is (C₁-C₄)alkyl or R⁴ and R⁵ taken together with N are a 5- or 6-membered heterocycloaliphatic ring, optionally substituted by (C₁-C₃)alkyl or comprising an additional ring O- or N-atom. The benzoic acid moiety can be the moiety (R²)(R³) ArCO₂H wherein Ar is an aromatic -C₆H₃- radical "phenylene" and (phenylene) and each R² and R³ is H, halo, preferably Cl, (R⁵)(H)N-, H₂N- or (C₁-C₅) alkoxy.

20 Useful topical anesthetics include lidocaine ((2-diethylamino)-N-(2,6-dimethylphenyl)-acetamide) (see Lofgren et al. (U.S. Patent No. 2,441,498), May & Baker (British Patent No. 706409) and Macfarlane & Co. (British Patent No. 758,224)); bupivacaine (1-butyl-N-(2,6-dimethylphenyl)-2-piperidinecarboxyamide) (see Thuresson et al., (U.S. Patent No. 2,955,111) and Sterling Drug (British Patent Nos. 1,166,802 and 1,180,712)); mepivacaine (2-piperidinecarboxyamide, N-(2,6-dimethylphenyl)-1-methyl), chloroprocaine (4-amino-2-chlorobenzoic acid 2-(diethylamino)ethyl ester); procaine (4-aminobenzoic acid 2-(diethylamino)ethyl ester); etidocaine (N-(2,6-dimethylphenyl)-2-(ethylpropylamino)butanamide; see, Astra (German Patent

No. 2162744)); tetracaine (4-(butylamino)benzoic acid 2-(dimethylaminoethyl ester; see Shupe (U.S. Patent No. 3,272,700)); benoxinate (4-amino-3-butoxybenzoic acid 2-(diethylamino)ethyl ester (U.K. Patent No. 654,484)) proparacaine (3-amino-4-propoxybenzoic acid 2-(diethylamino) ethyl ester); 5 dibucaine (3-butoxy-N-[2-(diethylamino)ethyl]-4-quinolinecarboxyamide; Miescher (U.S. Patent No. 1,825,623)); dyclonine (1-(4-butoxyphenyl)-3-(1-piperidinyl-1-propanone)); isobucaine (1-propanol, 2-methyl-2-[(2-methylpropyl)amino]benzoate; meprylcaine ([(2-methyl)(2-propylamino)propyl] benzoate); piperocaine ((2-methylpiperidin-1-ylpropyl(benzoate)); prilocaine (N-10 (2-methylphenyl)-2-(propylamino)propanamide); propoxycaine (2-(diethylamino)ethyl-([2'-methyl-4-amino]benzoate)); pyrrocaaine (1-(pyrrolidin-1-yl)-N-(2,6-dimethylphenyl)acetamide, butacaine (((3-dibutylamino)propyl)-(2'-aminobenzoate)); cyclomethylcaine (((3-(2'-methylproperidine-1-yl))propyl)-[4'-cyclohexyloxy-benzoate]); dimethylisoquin, diperodon, hexylcaine (((2'-cyclohexylamino)(1-methyl)ethyl)(benzoate); proparacaine (((2-diethylamino)ethyl) [(4'-propyloxyl-3'-amino)benzoate]); cocaine and its analogs (see, Carroll et al., *J. Med. Chem.*, 34, 2719 (1991); *Eur. J. Pharmacol.*, 184, 329 (1990); and the pharmaceutically acceptable salts thereof.

Preferred salts include the amine addition salts of inorganic and organic acids, e.g., the hydrochloride, hydrobromide, sulfate, oxalate, fumarate, citrate, 20 malate, propionate and phosphate salts. The hydrochloride and sulfate salts are preferred for use in the present invention.

These topical anesthetics and the salts thereof are discussed in detail in Remington's Pharmaceutical Sciences, A. Osol, ed., Mack Pub. Co., Easton, PA 25 (16th ed. 1980), and in The Merck Index (11th ed. 1989).

Glucocorticoids

Over 50 steroids have been shown to be present in the adrenal cortex. Only seven of these, however, have been shown to exert a significant biological effect related to adrenal cortical function. However, the adrenal cortex also 30 produces androgenic steroids. All of the adrenal cortical steroids, except the androgens, contain 21 carbon atoms, an α , β - unsaturated ketone in ring A, and

an α -ketol chain attached to ring D. They differ in extent of oxygenation or hydroxylation at carbons 11, 17, or 19.

Depending on whether the predominant biological effect is related to electrolyte and water metabolism, or to carbohydrate and protein metabolism, the 5 cortical steroids are classified as either mineralcorticoid or glucocorticoid, respectively. In general, clinical experience has indicated that the anti-inflammatory activity of adrenal cortical steroids in man correlates well with their glucocorticoid activity. The undesirable side effects (sodium retention, edema) are associated with mineralcorticoid activity.

10 Interest in glucocorticoids primarily focuses on their anti-inflammatory and immunosuppressant effects. Although the administration of glucocorticoids for their antiinflammatory effects is palliative therapy because the underlying cause of the disease remains, the suppression of inflammation and its consequences has made these agents of great value clinically - indeed, at times

15 lifesaving. The glucocorticoids are also of immense value in treating diseases that result from undesirable immune reactions. These diseases range from conditions that are predominantly the consequence of humoral immunity, such as idiopathic thrombocytopenia, to those that are mediated by cellular immune mechanisms, such as the rejection of transplanted organs. The

20 immunosuppressive and antiinflammatory actions of the glucocorticoids are inextricably linked because they both result in large part from inhibition of specific function of leukocytes. In several instances these effects on leukocytes are a consequence of glucocorticoid-induced inhibition of the elaboration and/or action of lymphokines.

25 Glucocorticoids useful in the practice of the present invention include, but are not limited to, beclomethasone dipropionate, betamethasone, betamethasone acetate, betamethasone sodium phosphate, betamethasone valerate, budesonide, cortisol, cortisol acetate, cortisol cypionate, cortisol sodium phosphate, cortisol sodium succinate, cortisone acetate, dexamethasone,

30 flumethasone pivalate, fluocinolone acetonide, fluocinonide, fluorometholone, flurandrenolide, fluticasone, meprednisone, methylprednisolone, methylprednisolone acetate, methylprednisolone sodium succinate,

paramethasone acetate, prednisolone, prednisolone acetate, prednisolone sodium phosphate, prednisolone sodium succinate, prednisolone succinate, prednisolone tebutate, triamcinolone, triamcinolone acetonide, triamcinolone diacetate, triamcinolone hexacetonide, amcinonide, betamethasone benzoate,

5 betamethasone dipropionate, clobetasone butyrate, clocortolone pivalate, cortisol butyrate, cortisol valerate, desonide, desoximetasone, and the like. These glucocorticoids and the salts thereof are discussed in detail in Remington's Pharmaceutical Sciences, A. Osol, ed., Mack Pub. Co., Easton, PA (16th ed. 1980).

10 Preferably, the glucocorticoid is beclomethasone, betamethasone, budesonide, cortisol, cortisone, dexamethasone, flumethasone, fluocinolone, fluocinonide, fluorometholone, flurandrenolide, fluticasone, meprednisone, methylprednisolone, prednisolone, triamcinolone, amcinonide, desonide, desoximetasone, or a pharmaceutically acceptable salt thereof. More preferably 15 the glucocorticoid is betamethasone, cortisol, cortisone, dexamethasone, meprednisone, methylprednisolone, or prednisolone or a pharmaceutically acceptable salt thereof. Most preferably, the glucocorticoid is dexamethasone or a pharmaceutically acceptable salt thereof. For example, dexamethasone salts useful in the practice of the present method include the tert-butylacetate, the 21-phosphate, 21-phosphate disodium salt, the tetrahydrophthalate, the 21-palmitate, 20 the 17,21-dipropionate, the 21-isonicotinate, and the 21-diethyl-amino-acetate salts of dexamethasone.

Administration and Dosages

The topical anesthetic or anesthetics and the glucocorticoid or 25 glucocorticoids (the "active ingredients") are co-administered so that they are both present at the active site (*in vivo*) in therapeutically effective amounts. Thus, the active ingredients may be combined either in the pure form or in combination with one or more pharmaceutically acceptable carriers in a single 30 composition. Alternatively, the active ingredients can be formulated as discrete compositions and administered concurrently, i.e., via a double lumen catheter, as encapsulated coated microparticles, via an inhaler with double outlets, or via like dosage forms. The active ingredients may also be administered sequentially, i.e.,

via the use of two discrete inhalers, injections, tablets or the like, administered so that the active ingredients both reach therapeutic levels together at the target site.

For example, the active ingredients may be administered as a single composition suitable for oral or parenteral (including intramuscular,

5 subcutaneous and intravenous) administration. Forms suitable for parenteral administration also include forms suitable for administration by inhalation or insufflation or for nasal, or topical (including buccal, rectal, vaginal and sublingual) administration. The active ingredients may, where appropriate, be conveniently presented in discrete unit dosage forms and may be prepared by
10 any of the methods well known in the art of pharmacy. Such methods include the step of bringing into association the active compound with liquid carriers, solid matrices, semi-solid carriers, finely divided solid carriers or combinations thereof, and then, if necessary, shaping the product into the desired delivery system.

15 Furthermore, compositions suitable for oral administration may be presented as discrete unit dosage forms such as hard or soft gelatin capsules, cachets or tablets each containing a predetermined amount of the active ingredients; as a powder or as granules; as a solution, a suspension or as an emulsion; or in a chewable base such as a synthetic resin for ingestion of the
20 active ingredients from a chewing gum. The active ingredients may also be presented as a bolus, electuary or paste. Tablets and capsules for oral administration may contain conventional excipients such as binding agents, fillers, lubricants, disintegrants, or wetting agents. The tablets may be coated according to methods well known in the art, i.e., with enteric coatings.

25 Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups or elixirs, or may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, emulsifying agents, non-aqueous vehicles (which may include edible
30 oils), or preservatives.

The active ingredients may also be formulated for parenteral administration (e.g., by injection, for example, bolus injection or continuous infusion) and may be presented in unit dose form in ampules, pre-filled syringes, small volume infusion containers or in multi-dose containers with an added preservative. The active ingredients may take such forms as suspensions, solutions, or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents. Alternatively, the active ingredients may be in powder form, obtained by aseptic isolation of sterile solid or by lyophilization from solution, for constitution with a suitable vehicle, e.g., sterile, pyrogen-free water, before use.

For topical administration to the epidermis, the active ingredients may be formulated as ointments, creams or lotions, or as the active ingredients of a transdermal patch. Suitable transdermal delivery systems are disclosed, for example, in A. Fisher et al. (U.S. Patent No. 4,788,603), or R. Bawa et al. (U.S. Patent Nos. 4,931,279; 4,668,506 and 4,713,224). Ointments and creams may, for example, be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling agents. Lotions may be formulated with an aqueous or oily base and will in general also contain one or more emulsifying agents, stabilizing agents, dispersing agents, suspending agents, thickening agents, or coloring agents. The active ingredients can also be delivered via iontophoresis, e.g., as disclosed in U.S. Patent Nos. 4,140,122; 4,383,529; or 4,051,842.

When desired, the above-described formulations can be adapted to give sustained release of the active ingredients employed, e.g., by combination with certain hydrophilic polymer matrices, e.g., comprising natural gels, synthetic polymer gels or mixtures thereof.

Compositions suitable for rectal administration wherein the carrier is a solid are most preferably presented as unit dose suppositories. Suitable carriers include cocoa butter and other materials commonly used in the art, and the suppositories may be conveniently formed by admixture of the active

compounds with the softened or melted carrier(s) followed by chilling and shaping in molds.

Compositions suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or sprays containing, in addition 5 to the active ingredients, such carriers as are known in the art to be appropriate.

The active ingredients may also be formulated so as to be suitable for administration by inhalation or insufflation or for nasal, intraocular or other topical (including buccal and sub-lingual) administration. For example, for administration to the upper (nasal) or lower respiratory tract by inhalation, the 10 active ingredients are conveniently delivered from an insufflator, nebulizer or a pressurized pack or other convenient means of delivering an aerosol spray. Pressurized packs may comprise a suitable propellant such as dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol, the 15 dosage unit may be determined by providing a valve to deliver a metered amount.

Alternatively, for administration by inhalation or insufflation, the active ingredients may take the form of a dry powder composition, for example, a powder mix of the active ingredients and a suitable powder base such as lactose 20 or starch. The powder composition may be presented in unit dosage form in, for example, capsules or cartridges or, e.g., gelatin or blister packs from which the powder may be administered with the aid of an inhalator, insufflator or a metered-dose inhaler.

For intra-nasal administration, the active ingredients may also be 25 administered via nose drops, a liquid spray, such as via a plastic bottle atomizer or metered-dose inhaler. Typical of atomizers are the Mistometer® (Wintrop) and the Medihaler® (Riker).

Drops, such as eye drops or nose drops, may be formulated with an aqueous or non-aqueous base also comprising one or more dispersing agents, 30 solubilizing agents or suspending agents. Liquid sprays are conveniently delivered from pressurized packs. Drops can be delivered via a simple eye

dropper-capped bottle, or via a plastic bottle adapted to deliver liquid contents dropwise, via a specially shaped closure.

The active ingredients may further be formulated for topical administration in the mouth or throat. For example, the active ingredients may 5 be formulated as a lozenge further comprising a flavored base, usually sucrose and acacia or tragacanth; pastilles comprising the composition in an inert base such as gelatin and glycerin or sucrose and acacia; and mouthwashes comprising the composition of the present invention in a suitable liquid carrier.

The formulations and compositions described herein may also contain 10 other ingredients such as antimicrobial agents, or preservatives. Furthermore, the active ingredients may also be used in combination with other therapeutic agents, for example, bronchodilators.

It will be further appreciated that the amount of a formulation comprising the active ingredients required for use in treatment will vary not only with the 15 particular topical anesthetic and glucocorticoid selected, but also with the route of administration, the nature of the condition being treated and the age and condition of the patient and will be ultimately at the discretion of the attendant physician or veterinarian. In general, however, a suitable unit dose of topical anesthetic for counteracting respiratory tract symptomatology will deliver from 20 about 0.05 to about 10-15 mg/kg, e.g., from about 0.10 to about 5.0 mg/kg of body weight per day. A suitable unit dose of glucocorticoid will deliver from about 0.050 to about 10-15 mg/kg, e.g., from about 0.10 to about 5.0 mg/kg of body weight per day.

The desired dose may conveniently be presented in a single dose or as 25 divided doses administered at appropriate intervals, for example, as two, three, four or more sub-doses per day. The sub-dose itself may be further divided, e.g., into a number of discrete, loosely spaced administrations such as multiple inhalations from an insufflator or by application of a plurality of drops into the eye or nose.

30 The invention will be further described by reference to the following detailed Examples.

Example 1 - Inhibition of IL-5-Mediated Eosinophil Survival by Lidocaine**A. Eosinophil Purification**

Eosinophils were purified from human peripheral blood, as previously described by Fujisawa et al., *J. Immunol.*, **144**, 642 (1990). Briefly, heparinized 5 (10 U/ml) venous blood was obtained from normal volunteers or patients with mild asthma or hay fever and sedimented with 6% dextran in 0.9% NaCl (Gentran 70) (Travenol Laboratories, Deerfield, IL) at 5:1 (v/v) ratio for 45 minutes at 37°C. The buffer coat was collected and washed twice in Pipes buffer (25 mM piperazine-N,N'-bis[2-ethanesulfonic acid], 110 mM NaCl, 5 mM KCL, 10 25 mM NaOH, 5.4 mM glucose, pH 7.4) with 50 U/ml DNase (Sigma Chemical Co., St. Louis, MO). The cells were suspended in 2.4 ml of Percoll (Sigma), density 1.070 g/ml, with 5% heat-inactivated defined calf serum (DCS) (Hyclone Laboratories, Logan, UT) and overlaid on a discontinuous Percoll gradient consisting of the following densities (g/ml): 1.080, 1.085, 1.090, 1.100, and 15 1.120. The osmolarity of Percoll ranged from 290 to 315 mOsm/kg and the pH was 7.4. Cells were centrifuged through the gradient at 1,500 g in a JA-20 fixed angle rotor on a Beckman J2-21 centrifuge at 4°C for 45 minutes. Fractions were collected and eosinophil numbers were determined utilizing Randolph's stain. Eosinophil-rich fractions were pooled, washed twice in Pipes buffer with 20 1% DCS, and used for experiments immediately. The eosinophil preparations were > 80% pure and > 98% viable, as determined by Randolph's stain and by trypan blue exclusion, respectively. The contaminating cells were neutrophils. There was no contamination by lymphocytes or monocytes.

B. Eosinophil-Survival Assay

25 Eosinophils were cultured at 37°C and 5% CO₂ in 200 µl Hydri-Care® medium containing gentamicin and 10% DCS in 90-well, flat-bottom tissue culture plates at a cell concentration of 2.5 x 10⁵/ml or 1.25 X 10⁵ cells/ml. No difference in viability was observed at these two cell concentrations. Viability was determined at day 4 for all experiments unless otherwise specified. A 30 Neubauer hemacytometer (C.A. Hausser & Son; Philadelphia, PA) and fluorescence microscopy were used to count live cells, stained green with fluorescein diacetate (Rotman et al., *PNAS USA*, **55**, 134 (1966)), and dead

cells, stained red with propidium iodide (Pullen et al., *J. Immunol. Methods* 43, 87 (1981)). Viability was calculated by the formula: viability % = (live cells)/(live cells + dead cells)) x 100%. Each experiment was performed in duplicate and all results represent three or more experiments.

5 C. Cytokine-mediated Eosinophil Survival and Effects of Topical Anesthetics

As reported by Wallen et al., *J. Immunol.*, 147, 3940 (1991), the responses of eosinophil survival to increasing concentrations of IL-5, IL-3, GM-CSF and IFN- γ were determined. For determination of the effect of lidocaine 10 and other topical anesthetics on cytokine-mediated survival, eosinophils were cultured in the presence of specified cytokine and topical anesthetic concentrations, and viability in the presence of the test anesthetic was compared to viability in cytokine-enriched medium alone. Anesthetics were dissolved in 0.15 M NaCl, stored at -20°C, and diluted in medium just before use; thus, 0.15 15 M NaCl was used as a control for each experiment. The effects of the anesthetics and the vehicle control on cytokine-mediated viability were tested. Inhibition of viability was determined by the formula: inhibition % = ($V_{med} - V_{an}$)/ V_{med} x 100%, where V_{med} = viability in cytokine enriched medium alone and V_{an} = viability at the specified anesthetic and cytokine concentrations. IC_{50} is the 20 concentration of anesthetic that produces 50% inhibition of viability. The change in dose-response to cytokine in the presence of varied lidocaine concentrations was tested and the EC_{50} for each lidocaine concentration was calculated. EC_{50} is the IL-5 concentration that produces 50% enhancement of viability; the 50% viability enhancement was determined by subtracting the 25 baseline viability from the maximum viability and dividing the difference by two, or $V_{50} = (V_{max} - V_{min})/2$, where V_{max} = viability achieved with optimum cytokine concentration and V_{min} = viability in the absence of cytokine and anesthetic. For determination of the time course of the anesthetic effect, medium was supplemented with rhIL-5, 220 fM, or 890 fM, and the effects of anesthetic 30 1000 nM, 100 nM, or control were tested by comparing viability at 1, 2, and 4 days in the presence or absence of anesthetic.

D. Statistics

All values are expressed at the mean \pm SEM and represent three or more experiments performed in duplicate. Significance of differences in viability were determined using a one-tailed Student's *t*-test.

5 E. Results

As shown in Figure 1, when 10 pg/ml IL-5 was used in eosinophil culture, significant inhibition by lidocaine was not seen until day 4 of incubation. Second, as shown in Figure 2, the eosinophil survival inhibition produced by lidocaine was largely overcome by high concentrations of IL-3 and GM-CSF, but 10 not by IL-5.

Example 2 - Inhibition of Eosinophils By Local Anesthetics

To determine whether or not other topical anesthetics, particularly those of the carboxamide (lidocaine) class or benzoate class, also can inhibit eosinophil viability *in vitro*, the assay of Example 1(C) was carried out. 15 Eosinophils were cultured in the presence of 100 pg/ml IL-5 and 1 mM/ml, 0.1 mM/ml and 0.01 mM/ml of lidocaine and nine other topical anesthetics, and viability in the presence of the anesthetic was compared to viability in medium with and without IL-5. The results of this study are summarized on Table 1, below.

Table 1

IL-5	Local Anesthetic 1 mM/ml	Viable Eosinophils on Day 4 ($x \pm SD$)
5	100 pg/ml	Lidocaine 10 ± 2
	100 pg/ml	Bupivacaine 0 ± 0
	100 pg/ml	Chloroprocaine 54 ± 13
	100 pg/ml	Etidocaine 0 ± 0
10	100 pg/ml	Procaine 59 ± 22
	100 pg/ml	Tetracaine 0 ± 0
	100 pg/ml	Benoxinate 0 ± 0
	100 pg/ml	Proparacaine 27 ± 8
15	100 pg/ml	Dibucaine 0 ± 0
	100 pg/ml	Dyclonine 0 ± 0
	10 pg/ml	None 78 ± 8
	None	None 69 ± 7
20	None	None 22 ± 11

As described above, in the eosinophil survival assay, eosinophils are cultured in the absence and the presence of a survival stimulating factor, such as interleukin (IL)-5. In Table 1, eosinophil viability was enhanced over culture medium by addition of 10 or 100 pg/ml of IL-5. For example, the survival of eosinophils in the absence of any survival-enhancing factor was 22% (78% of the eosinophils were dead) at four days. In the presence of IL-5, the survival of eosinophils was increased to 78% by 100 pg/ml of IL-5. In the presence of 100 pg/ml of IL-5, 1 mM of lidocaine inhibited eosinophil survival, such that only 10% of the cells were viable at day 4. Similarly, bupivacaine, etidocaine, tetracaine, benoxinate, dibucaine and dyclonine strikingly inhibited eosinophil survival, suggesting that they were as potent, if not more potent, than lidocaine. In addition, proparacaine also showed weak IL-5 inhibitory activity reducing eosinophil survival from an expected 78% (in the presence of IL-5, 100 pg/ml) to 27%. These data indicate that numerous topical anesthetics have potent effects on eosinophil survival and appear to exhibit a bioactivity which is comparable to that exhibited by lidocaine.

Example 3 - Treatment of Bronchial Asthma with Lidocaine

Glucocorticoids are believed to be effective to manage bronchial asthma due to their ability to interfere with the cytokine-indicated accumulation and activation of inflammatory cells, including eosinophils. Examples 1-2 indicate

that lidocaine and other topical anesthetics are able to mimic the bioactivity of glucocorticoids. Therefore, lidocaine was evaluated for its ability to replace glucocorticoids in the therapy of bronchial asthma.

A. Patient A

5 Patient A is a woman (age 43) presenting with chronic, severe, glucocorticoid-dependent bronchial asthma. This patient was begun on lidocaine inhalation (2% aqueous lidocaine, 2 ml per nebulization, four times a day) delivered via a deVilbiss nebulizer (Model #5610D). Nebulization of this concentration of lidocaine has not caused side effects other than transient 10 numbness of the oral cavity and of the upper regions of the pharynx and larynx, and this was well tolerated.

Patient A was begun on lidocaine inhalation in early September 1992, at a time when she was receiving 40 mg of prednisone orally a day, as well as 20 puffs of asthmacort (triamcinolone). Over the preceding four months, the patient 15 had received virtually continuous prednisone therapy. The lowest dose administered was 5 mg daily for a period of a few days in the middle of June 1992. After that reduction in therapy, the patient required a prompt increase in the quantity of glucocorticoids to 40 mg daily and then a taper was done such that she received 40 mg on one day and gradually decreasing doses of prednisone 20 on the alternate day. As shown in Figure 3, the patient eventually reached a dose of 20 mg prednisone on one day and no prednisone on the following day, but this regimen was followed by a severe flare of asthma, such that for a period of time in July, she required therapy with 80 mg of prednisone a day.

Initiation of lidocaine therapy in late September was associated with a 25 reduction in the patient's nocturnal cough and with relief of the patient's breathlessness. The prior prednisone therapy, while keeping the asthma under control, did not completely relieve the symptoms, whereas lidocaine therapy was associated with a feeling of well being and virtually complete relief of symptoms. Following initiation of lidocaine therapy, the patient's prednisone 30 was reduced gradually, such that by December 1992, the patient was receiving 5 mg every other day, a dose which she had not been able to achieve other than briefly in June 1992. In mid-November, an exacerbation of asthma occurred

following a respiratory tract infection, which was treated by addition to the patient's therapy of one administration of 80 mg of prednisone.

B. Patient B

5 Patient B is a woman (age 34), who was begun on lidocaine therapy around the middle of September 1992, as described in section A, above. As shown by Figure 4, she has been able to reduce prednisone therapy from an average of 50 mg daily to a dose of 5 mg daily in early December 1992. This reduction has not been associated with any untoward effects other than those which one anticipates from reduction of glucocorticoids in any patient who has
10 been receiving glucocorticoids for long periods of time. (Glucocorticoid withdrawal causes a characteristic syndrome associated with malaise and muscle aching; both patients A and B have experienced these symptoms).

Example 4 - The Effects of Lidocaine and Dexamethasone on Isolated Human Eosinophils

15 The effects of lidocaine and dexamethasone on isolated human eosinophils was determined utilizing an *in vitro* assay of eosinophil survival. In the below described experiment, all drugs were purchased from Sigma. Human recombinant IL-5 was generously provided by Shering-Plough Corporation. Lidocaine was resuspended in Hybri-Care media with 10% alpha calf serum and
20 made fresh for each use. Dexamethasone was resuspended in DMSO, and dilutions of the dexamethasone stock solution were made in Hybri-Care® medium supplemented with 10% alpha calf serum. The concentration of DMSO in the dexamethasone solutions added to the eosinophils never exceeded 0.001%.

A. Eosinophil Isolation

25 Human eosinophils were isolated by layering over Percoll and separation from remaining neutrophils by negative selection using anti-CD16 magnetic beads and MACS column isolation, as previously described by Ide et al., J. Immunol. Methods, 168, 187 (1994). The isolated eosinophils were >97% pure.

B. Eosinophil-Survival Assay

30 Isolated eosinophils were incubated in 96-well plates at 2.5×10^5 /mL with varying concentrations of IL-5 plus or minus drugs in a total volume of 200 μ L. The eosinophils were incubated for 4 days at 37°C and 5% CO₂. To

determine percent survival, the total volume of each well was transferred to a separate 12 x 75 polystyrene tube and stained with 200 μ l of a 0.5 mg/mL propidium iodide (PI) solution. The sample was then analyzed on a Becton Dickinson FACScan flow cytometer for PI fluorescence. The percentage of 5 surviving eosinophils is defined as the number of PI-negative eosinophils over the total number of eosinophils gated and analyzed.

C. Results

As shown in Figure 5, the synergistic effect of combinations of 1 mM lidocaine (LC) with dexamethasone on eosinophil survival is apparent at 0.1 μ M 10 dexamethasone. Lower concentrations of LC may synergize with dexamethasone at lower concentrations of IL-5, but the most striking results were evident at 1000 pg/mL IL-5.

It will be apparent to one of ordinary skill in the art that many changes and modifications can be made in the invention without departing from the scope 15 of the appended claims.

WHAT IS CLAIMED IS:

1. A method for treating an eosinophil-associated pathology comprising co-administering to a mammal in need of such treatment an amount of a topical anesthetic and an amount of a glucocorticoid, wherein said amounts are effective to counteract at least one of the symptoms of said pathology.
2. The method of claim 1 wherein the mammal is a human.
3. The method of claim 1 wherein the pathology is bronchial asthma, eosinophil-associated intranasal inflammation, inflammation of the paranasal sinuses, allergic rhinitis, eosinophil-associated cutaneous inflammation, eosinophil-associated disorders of the gastrointestinal tract or eosinophil-associated inflammation of the eye.
4. The method of claim 3 wherein the pathology is bronchial asthma.
5. The method of claim 1 wherein the topical anesthetic and the glucocorticoid are administered to the respiratory tract of said human, by spraying or by nebulization.
6. The method of claim 5 wherein the topical anesthetic is administered in combination with a pharmaceutically acceptable liquid vehicle.
7. The method of claim 1 wherein the topical anesthetic is administered at a daily dose of about 0.05 - 15 mg/kg.
8. The method of claim 1 wherein the topical anesthetic is an N-arylamide aminoalkylbenzoate or a pharmaceutically acceptable salt thereof.
9. The method of claim 1 wherein the topical anesthetic is an aminoalkylbenzoate or a pharmaceutically acceptable salt thereof.

10. The method of claim 8 wherein the topical anesthetic is an N-(C₇-C₂₂) arylamide of an amino-substituted (C₁-C₅) - carboxylic acid or a pharmaceutically acceptable salt thereof.
11. The method of claim 10 wherein the topical anesthetic is an N-[(mono- or di-(C₁-C₄) alkyl) phenyl]amide of an aliphatic (C₁-C₅) carboxylic acid, wherein said acid is substituted with (R)(R¹)N-, wherein R is H or (C₁-C₅)alkyl and R¹ is (C₁-C₅) alkyl; or a pharmaceutically acceptable salt thereof.
12. The method of claim 11 wherein the topical anesthetic is lidocaine, prilocaine, or etidocaine or a pharmaceutically acceptable salt thereof.
13. The method of claim 12 wherein the topical anesthetic is lidocaine or lidocaine hydrochloride.
14. The method of claim 9 wherein the topical anesthetic is an ester between a carboxylic acid of the general formula:
$$(R^2)(R^3)ArCO_2H,$$
wherein Ar is C₆H₅ and each R² and R³ is H, halo, (R⁵)(H)N-, H₂N-, or (C₁-C₅)alkyl, and an alcohol of the general formula:
$$(R^4)(R^5)N(X)OH$$
wherein X is a branched- or straight-chain (C₁-C₅)alkylene; R⁴ is H or (C₁-C₄) alkyl, R⁵ is (C₁-C₄)alkyl or R⁴ and R⁵ taken together with N are a 5- or 6-membered heterocycloaliphatic ring, optionally substituted by (C₁-C₃) alkyl or comprising an additional ring O- or N- atom, or a pharmaceutically acceptable salt thereof.
15. The method of claim 14 wherein the topical anesthetic is procaine, chloroprocaine, dyclonine, tetracaine, benoxinate, proparacaine, meprylcaine, piperocaine or a pharmaceutically acceptable salt thereof.

16. The method of claim 1 wherein the topical anesthetic is bupivacaine, dibucaine or a pharmaceutically acceptable salt thereof.
17. The method of claim 1 wherein the glucocorticoid is beclomethasone, betamethasone, budesonide, cortisol, cortisone, dexamethasone, flumethasone, fluocinolone, fluocinonide, fluorometholone, flurandrenolide, fluticasone, meprednisone, methylprednisolone, prednisolone, triamcinolone, amcinonide, desonide, desoximetasone, or a pharmaceutically acceptable salt thereof.
18. The method of claim 17 wherein the glucocorticoid is betamethasone, cortisol, cortisone, dexamethasone, meprednisone, methylprednisolone, or prednisolone, or a pharmaceutically acceptable salt thereof.
19. The method of claim 18 wherein the glucocorticoid is dexamethasone, or a pharmaceutically acceptable salt thereof.
20. The method of claim 1 wherein said amounts are co-administered simultaneously.
21. The method of claim 20 wherein a pharmaceutical composition is administered comprising the amount of said topical anesthetic and the amount of said glucocorticoid.
22. The method of claim 20 wherein a first pharmaceutical composition comprising said topical anesthetic in combination with a pharmaceutically acceptable carrier is administered simultaneously with a second pharmaceutical composition comprising said glucocorticoid in combination with a pharmaceutically acceptable carrier.
23. The method of claim 1 wherein said amounts are administered sequentially.

24. The use of a combination of a topical anesthetic and a glucocorticoid to prepare a medicament for treating an eosinophil-associated pathology in a mammal.
25. Claim 24 wherein the mammal is a human.
26. Claim 24 wherein the pathology is bronchial asthma, eosinophil-associated intranasal inflammation, inflammation of the paranasal sinuses, allergic rhinitis, eosinophil-associated cutaneous inflammation, eosinophil-associated disorders of the gastrointestinal tract or eosinophil-associated inflammation of the eye.
27. Claim 26 wherein the pathology is bronchial asthma.
28. Claim 24 wherein the topical anesthetic is an N-arylamide aminoalkylbenzoate or a pharmaceutically acceptable salt thereof.
29. Claim 24 wherein the topical anesthetic is an aminoalkylbenzoate or a pharmaceutically acceptable salt thereof.
30. Claim 28 wherein the topical anesthetic is an N-(C₇-C₂₂) arylamide of an amino-substituted (C₁-C₅) - carboxylic acid or a pharmaceutically acceptable salt thereof.
31. Claim 30 wherein the topical anesthetic is an N-[(mono- or di-(C₁-C₄) alkyl) phenyl]amide of an aliphatic (C₁-C₅) carboxylic acid, wherein said acid is substituted with (R)(R¹)N-, wherein R is H or (C₁-C₅)alkyl and R¹ is (C₁-C₅) alkyl; or a pharmaceutically acceptable salt thereof.
32. Claim 31 wherein the topical anesthetic is lidocaine, prilocaine, or etidocaine or a pharmaceutically acceptable salt thereof.

33. Claim 32 wherein the topical anesthetic is lidocaine or lidocaine hydrochloride.
34. Claim 29 wherein the topical anesthetic is an ester between a carboxylic acid of the general formula:
$$(R^2)(R^3)ArCO_2H,$$
wherein Ar is C_6H_5 and each R^2 and R^3 is H, halo, $(R^5)(H)N^-$, H_2N^- , or $(C_1-C_5)alkyl$, and an alcohol of the general formula:
$$(R^4)(R^5)N(X)OH$$
wherein X is a branched- or straight-chain $(C_1-C_5)alkylene$; R^4 is H or $(C_1-C_4)alkyl$, R^5 is $(C_1-C_4)alkyl$ or R^4 and R^5 taken together with N are a 5- or 6-membered heterocycloaliphatic ring, optionally substituted by $(C_1-C_3)alkyl$ or comprising an additional ring O- or N- atom, or a pharmaceutically acceptable salt thereof.
35. Claim 34 wherein the topical anesthetic is procaine, chloroprocaine, dyclonine, tetracaine, benoxinate, proparacaine, meprylcaine, piperocaine or a pharmaceutically acceptable salt thereof.
36. Claim 24 wherein the topical anesthetic is bupivacaine, dibucaine or a pharmaceutically acceptable salt thereof.
37. Claim 24 wherein the glucocorticoid is beclomethasone, betamethasone, budesonide, cortisol, cortisone, dexamethasone, flumethasone, fluocinolone, fluocinonide, fluorometholone, flurandrenolide, fluticasone, meprednisone, methylprednisolone, prednisolone, triamcinolone, amcinonide, desonide, desoximetasone, or a pharmaceutically acceptable salt thereof.
38. Claim 37 wherein the glucocorticoid is betamethasone, cortisol, cortisone, dexamethasone, meprednisone, methylprednisolone, or prednisolone, or a pharmaceutically acceptable salt thereof.

39. Claim 38 wherein the glucocorticoid is dexamethasone, or a pharmaceutically acceptable salt thereof.
40. A pharmaceutical composition comprising a combination of a glucocorticoid and a topical anesthetic in an amount effective to counteract at least one of the symptoms of an eosinophil-associated pathology.

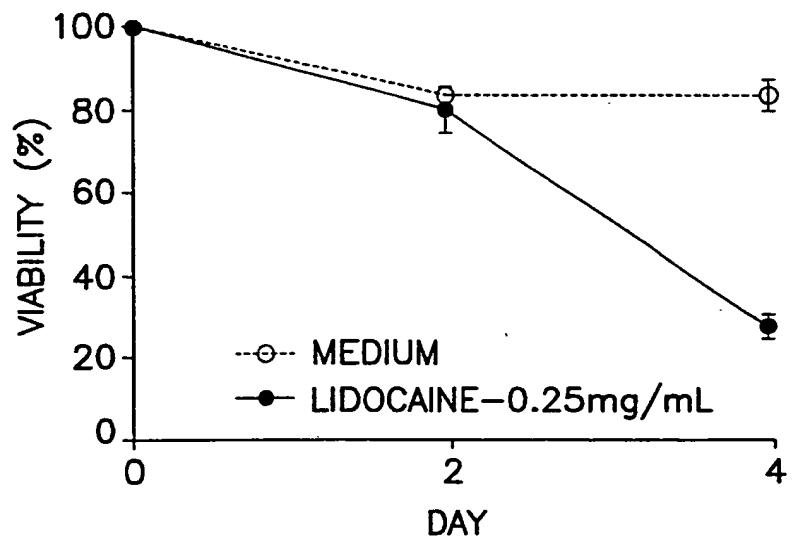


FIG. 1

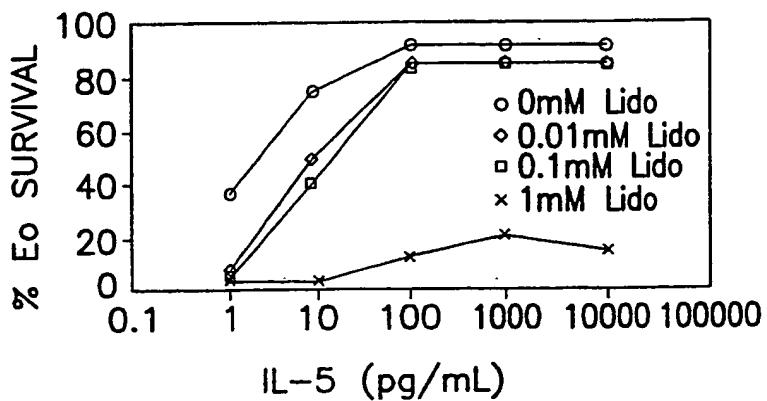


FIG. 2A

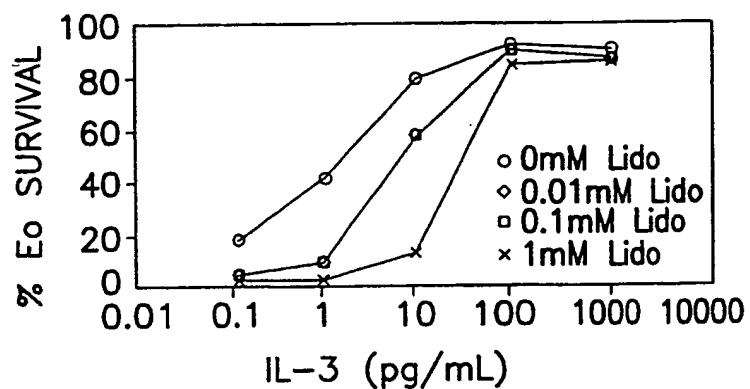


FIG. 2B

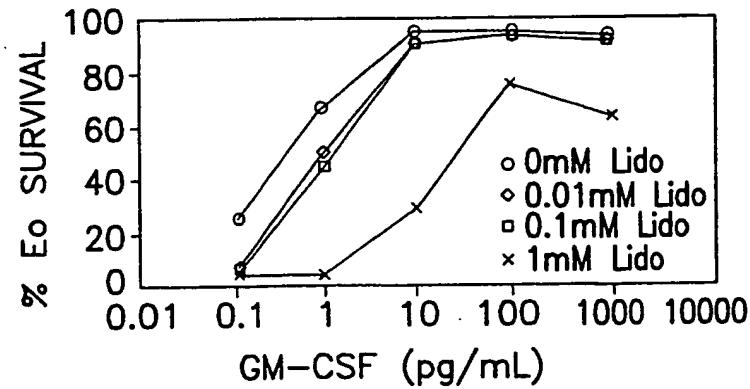


FIG. 2C

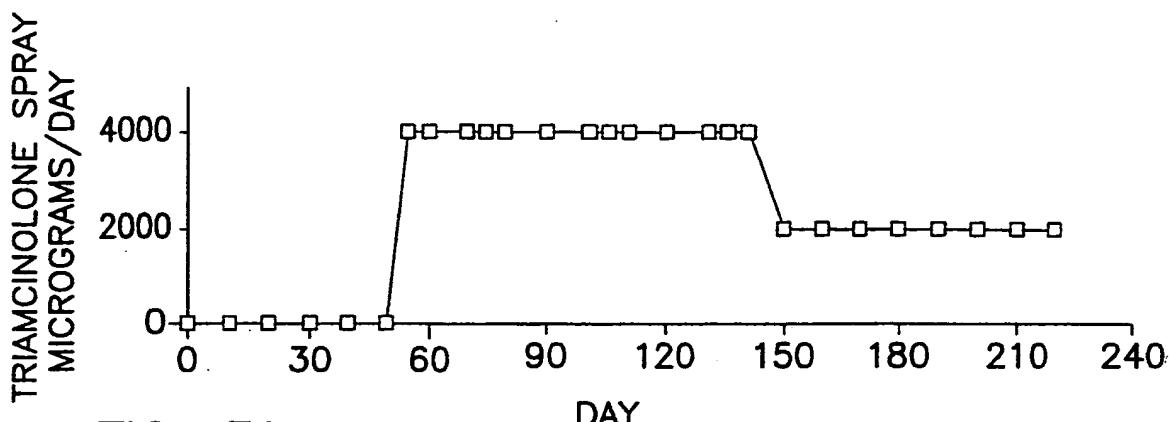


FIG. 3A

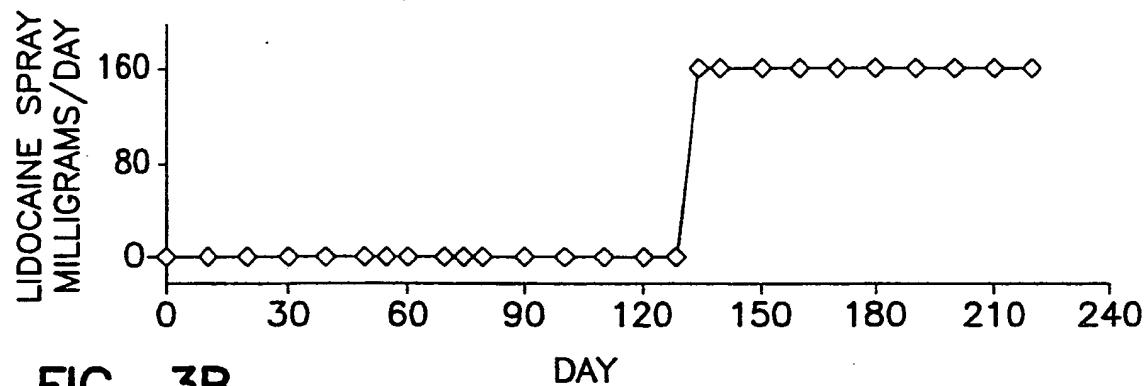


FIG. 3B

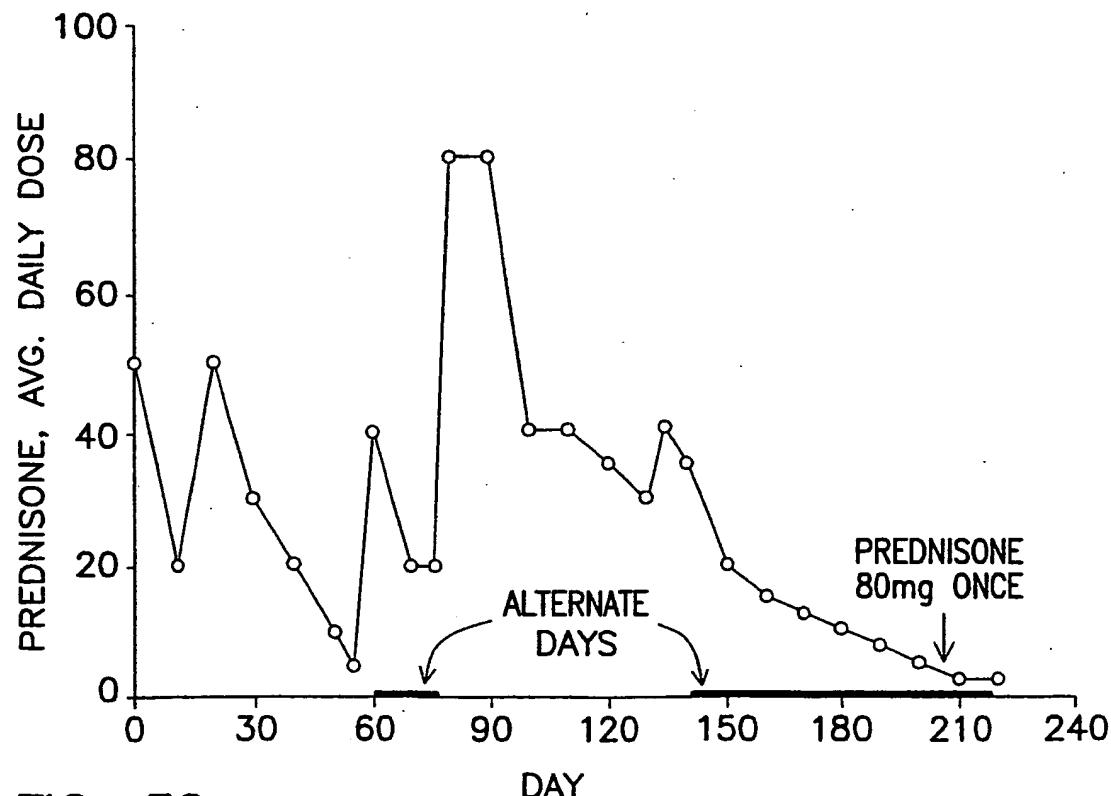


FIG. 3C

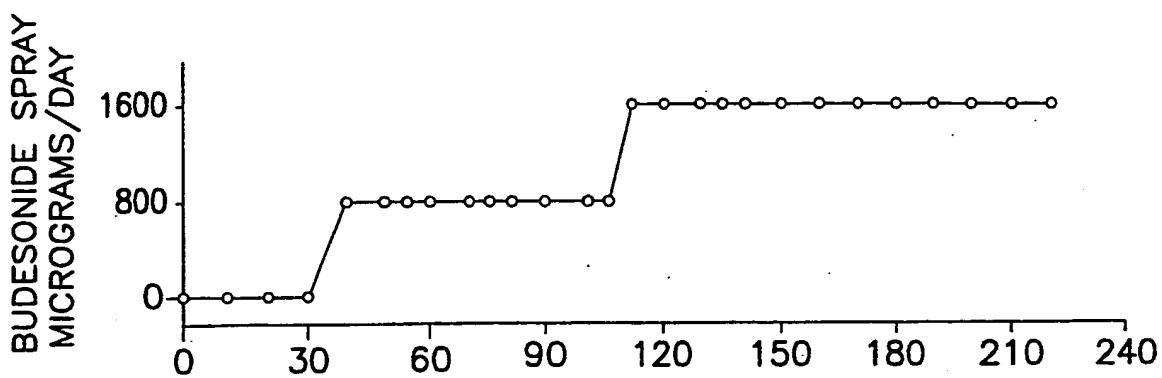


FIG. 4A

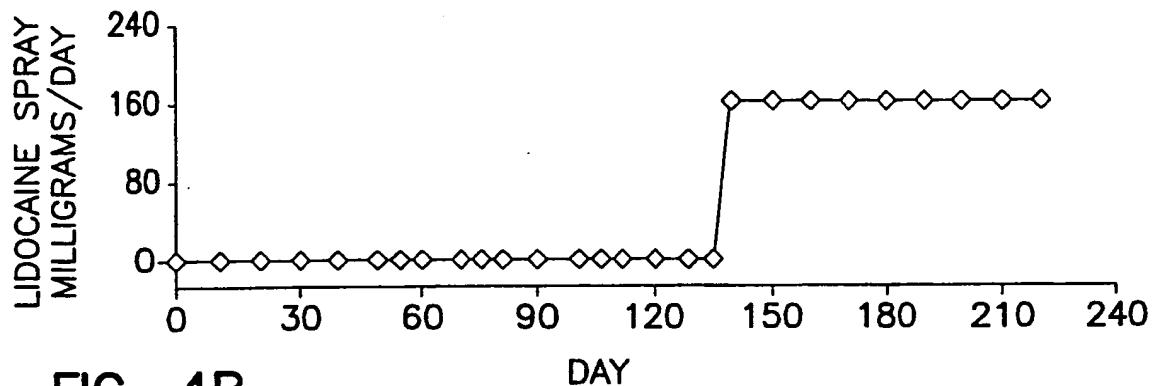


FIG. 4B

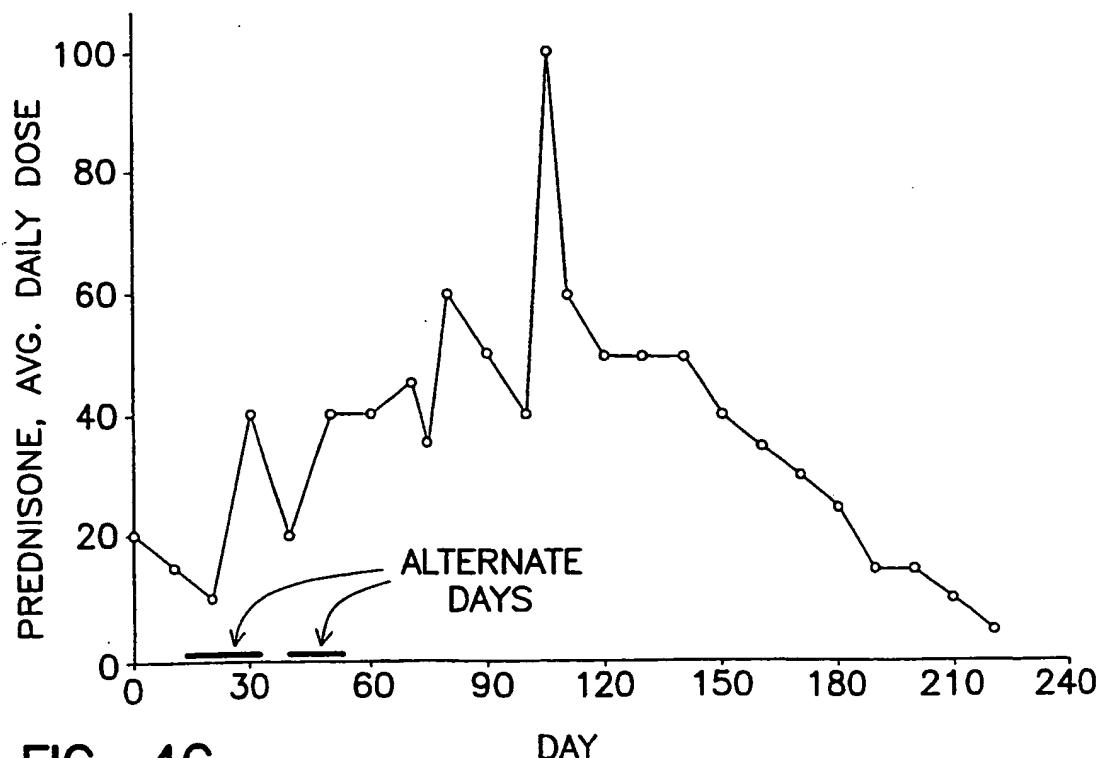


FIG. 4C

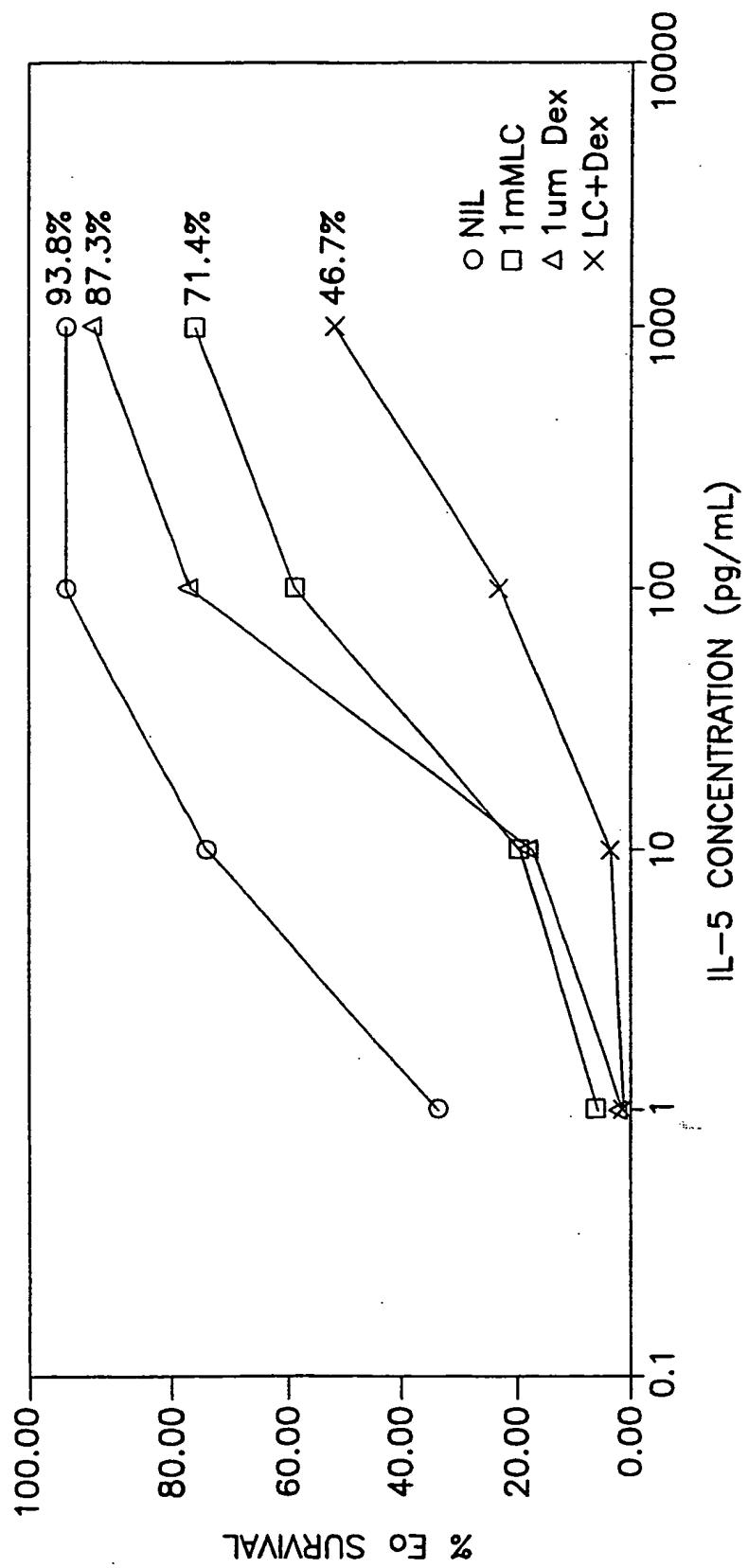


FIG. 5

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/57

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 510 339 A (MAYO FOUNDATION FOR MEDICAL EDUCATION AND RESEARCH) 23 April 1996 cited in the application see column 5, line 26-30; example 3 see column 4, line 43-65; claims see column 3, line 28-54 ---	1-17,20, 22-37,40
X	HUNT ET AL: "Effect of Nebulized Lidocaine on Severe Glucocorticoid-Dependent Asthma" MAYO CLINIC PROCEEDINGS, vol. 71, 1996, pages 361-368, XP002069072 see page 362; table 1 see page 367, left-hand column ---	1-13,20, 22-33,40



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

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Date of the actual completion of the international search

23 June 1998

Date of mailing of the international search report

22.07.98

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Fax: (+31-70) 340-3016

Authorized officer

Kanbier, D

C(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	OHNISHI ET AL: "Lidocaine in Bronchoalveolar Lavage Fluid (BALF) is an Inhibitor of Eosinophil-Active Cytokines" CLINICAL AND EXPERIMENTAL IMMUNOLOGY, vol. 104, 1996, pages 325-331, XP002069073 see page 330, left-hand column, paragraph 4 see page 326, left-hand column, paragraph 2 ---	1-5, 8-15,17, 18, 24-35, 37,38
X	US 4 866 050 A (BEN-AMOZ DANIEL) 12 September 1989 see column 2, line 30-42; claims 1-3,6,7 see column 3, line 26-34 see column 4, line 45-50 ---	1-4, 8-13, 16-21, 24-33, 36-40
X	US 5 008 289 A (GALENPHARMA INC) 16 April 1991 see column 1, line 52-61; claims 1,2 see column 2, line 16-22 ---	1-3, 6-14, 17-21, 24-26, 28-34, 37-40
X	WO 96 34599 A (CHILDRENS MEDICAL CENTER) 7 November 1996 see page 25, line 32 - page 26, line 15; claims 1,6,7,10,17,20; examples 2,3 ---	40 1,2, 8-21,24, 25,28-39
X	DATABASE WPI Week 8408. Derwent Publications Ltd., London, GB; AN 84-046979 XP002069074 & RO 82 578 (INTR ANTIBIOTICE) , 30 August 1983 see abstract & RO 82 578 A (INTR ANTIBIOTICE) -----	40 1,24

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 98/02960

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 1-40 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

Information on patent family members

PCT/US 98/02960

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
US 5510339	A 23-04-1996	AU 685777 B AU 6128294 A CA 2155200 A EP 0682514 A JP 8505157 T NZ 261990 A WO 9417790 A US 5631267 A		29-01-1998 29-08-1994 18-08-1994 22-11-1995 04-06-1996 22-08-1997 18-08-1994 20-05-1997
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WO 9634599	A 07-11-1996	US 5700485 A AU 5720796 A EP 0825853 A		23-12-1997 21-11-1996 04-03-1998

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